与非编码调节相关的抗动脉粥样硬化机制 中药活性单体的RNA

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Anti-atherosclerosis mechanisms associated with regulation of non-coding RNAs by active monomers of traditional Chinese medicine

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Guoqing Liu: Conceptualization, Methodology, Data curation, Writing – original draft. **Liqiang Tan:** Writing – review & editing. **Xiaona Zhao:** Data curation. **Minghui Wang:**Software, Methodology, Data curation. **Zejin Zhang:** Data curation. **Jing Zhang:** Methodology, Software, Validation.**Honggang Gao:** Data curation. **Meifang Liu:** Writing – review & editing. **Wei Qin:** Conceptualization, Writing – review& editing, Supervision, Funding acquisition. All authors have read and approved the final manuscript.

Declaration of competing interest

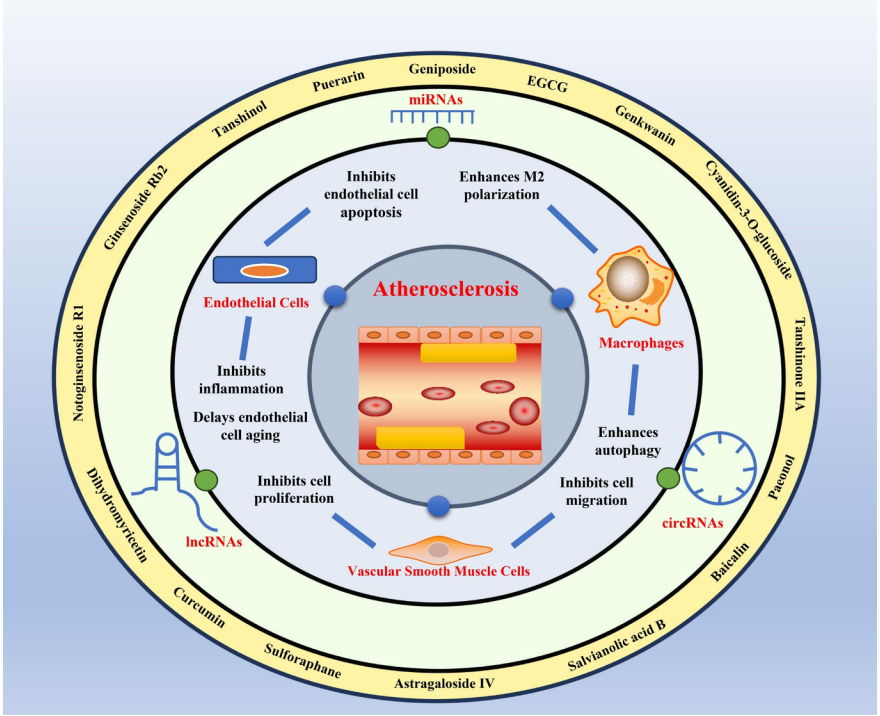
The authors declare that there are no conflicts of interest.

Abstract

Atherosclerosis is the leading cause of numerous cardiovascular diseases with a high mortality rate. Non-coding RNAs (ncRNAs), RNA molecules that do not encode proteins in human genome transcripts, are known to play crucial roles in various physiological and pathological processes. Recently, researches on the regulation of atherosclerosis by ncRNAs, mainly including microRNAs, long non-coding RNAs, and circular RNAs, have gradually become a hot topic. Traditional Chinese medicine has been proved to be effective in treating cardiovascular diseases in China for a long time, and its active monomers have been found to target a variety of atherosclerosis-related ncRNAs. These active monomers of traditional Chinese medicine hold great potential as drugs for the treatment of atherosclerosis. Here, we summarized current advancement of the molecular pathways by which ncRNAs regulates atherosclerosis and mainly highlighted the mechanisms of traditional Chinese medicine monomers in regulating atherosclerosis through targeting ncRNAs.

Key words: non-coding RNAs; traditional Chinese medicine; atherosclerosis; cardiovascular diseases; active monomer

Graphical abstract:



1 Introduction

动脉粥样硬化的特征是 具有极高发病率和死亡率的动脉(Libby 等人, 2019). 动脉粥样硬化是 脑血管和脑心血管疾病,Ru Nao Geng Sai , Guan Xin Bing He Xin Ji Geng Sai (Li Bi ,2021 年). Na Li Shi Dong Mai Zhou Yang Ying Hua De Xu Duo Yuan Yin ,Li Ru Yan Zheng Fan Ying (Y. 朱等人,2018 年), Xi Bao Si Wang He Shuai Lao (Baziioti 等人,2022 年),Yi Ji Nei Pi Dao Jian Chong Zhi Zhuan Hua (Liang 等人,2022 年),Qi Zhong Man Xing Yan Zheng Shi Jing Chang Bei Yan Jiu De Yuan Yin Guo Qu Ji Nian . Zai Fen Zi Shui Ping Shang ,Duan Li Sun Shang ,Ji Yin Zu DNA 损伤,Xian Li Ti DNA损伤积聚在血管内皮 细胞,You Dao Nei Pi Xi Bao Lao Hua He Man Xing Yan Zheng . Chi Xu Yan Zheng Dao Zhi Lin Ba Xi Bao Dui Ji Zeng Jia He Ju Shi Xi Bao ,Dao Zhi Dong Mai Zhou Yang Ying Hua (Okuyama等人,2015; 鲁帕雷利亚和乔杜里,2020 年;J. C. Wang & Bennett, 2012)。这 动脉粥样硬化的发病机制和治疗靶点早已存在 心血管研究领域的重点。他汀类药物、抑制剂 羟甲基戊二酰辅酶A(HMG-CoA)还原酶,Shi Qiang Xiao Jiang Dan Gu Chun Yao Wu He Zui Chang Yong De Lin Chuang Yao Wu Yu Fang He Zhi Liao Dong Mai Zhou Yang Ying Hua De Yao Wu (Ao Shan Deng) Deng Ren ,2015 年). Ta Ting Lei Yao Wu Ke Jiang Di Xin Xie Guan Ji Bing . Ran Er ,Ta Ting Lei Yao Wu Ke Neng Hui Ying Xiang Yao Wu Xiang Hu Zuo Yong ,Yin Wei Bu Tong De An Quan Xing He Nai Shou Xing ,Te Bie Shi Dang Yu Qi Ta Xin Xie Guan Yao Wu Lian He Shi Yong ,Zhe Jiang Dao Zhi Ta Ting Lei Yao Wu Xiang Guan Xing Gan Du Xing He Ji Bing De Feng Xian Zeng Jia (Bellosta和Corsini,2018)。因此,Po Qie Xu Yao Fa Xian Xin De Dong Mai Zhou Yang Ying Hua De Zhi Liao Ba Dian He Xin Yao .

Bu Ru Dong Wu Xi Bao Zhong De RNA很复杂,Qi Zhong [?] Xie Ju You Bian Ma Dan Bai Zhi ,Dan Qi Zhong [?] Xie Que Fa Ci Gong Neng . Mu Qian , Que Fa Bian Ma Dan Bai Zhi Gong Neng De RNA被命名为非编码 RNA(ncRNA),其中研究最多的是microRNA(miRNA),长 非编码RNA(lncRNA)和环状RNA(circRNA)(桥, Dao La Jia La ,He Ku Er Di Di Si ,2021 年;陈立等人,2021;Lu & Rothenberg, 2018). NcRNA已被证明在 动脉粥样硬化通过影响炎症反应的发病机制, Xi Bao Huo Hua He Zeng Zhi ,Yi Ji Zhi Zhi Dai Xie (Aryal & 苏亚雷斯,2019;范伯格和摩尔,2016)。如今,Zhi Liao Ce Lue Ba Xiang ncRNA已进入临床试验阶段 治疗癌症,Bei Ren Wei Shi [?] Chong You Xi Yin Li De Fang Fa Yong Yu Zhi Liao Dong Mai Zhou Yang Ying Hua .

Zi Gu Yi Lai ,Xu Duo Cao Yao Yi Bei Yong Yu Dong Mai Zhou Yang Ying Hua Xiang Guan Ji Bing De Zhi Liao He Jian Zhu Shi Zhu Yao De Lin Chuang Shi Yong De Chuan Tong Zhong Yao Xing Shi . Sui Zhao Fen Chi Ji Zhu De Fa Zhan ,Shi Fen Chi Cheng Wei Ke Neng Geng Duo Lai Zi Zhong Guo Fan Ti De Yao Li Huo Xing Dan Ti Yao . Zhe Shi Yan Jiu Ren Yuan Neng Gou Dui Te Ding De Dan Ti Er Bu Shi Zheng Ge Yao Yong Zhi Wu . Zai Mu Qian ,Yan Jiu Fa Xian ,Xu Duo Chuan Tong De Huo Xing Dan Ti Zhong Yi Dui Dong Mai Zhou Yang Ying Hua You Ji Ji Zuo Yong ,Ru Zao Gan (Luo, Chen, Su, & Zha, 2022), 黄酮类化合物 (Park et al., 2006) 和生物碱(Y. 李等人,2021 年). Li Ru ,Xiao Bo Jian ,[?] Chong Huo Xing Cong 小檗中提取的成分,Ke Yi Ji Huo Ju Shi Xi Bao Zhong De PPAR-γ通路,Dao Zhi Yan Zheng Yin Zi ,Ru Dan He Xi Bao Hua Xue Yin You Dan Bai -1 (MCP-1) 和 肿瘤坏死因子-α(TNF-α)(F. L. Chen等人,2008)。另一项研究 发现羟基红花黄A,一种来自红花的天然化合物,Dui Dong Mai Zhou Yang Ying Hua Tong Guo Yi Zhi Xie Guan Nei Pi Xi Bao Gong Neng Zhang Ai , Xie Guan Ping Hua Ji Xi Bao Zeng Zhi He Qian Yi ,Pao Mo Xi Bao Xing Cheng He Xie Xiao Ban Huo Hua (Xue等人,2021 年). Zhe Xie Huo Yue De Yu Ji Zhong Yao Dan Ti Han Liang Gao Dong Mai Zhou Yang Ying Hua Zhi Liao De Zhi Liao Qian Li . Ran Er , Zhe Xie Huo Xing Cheng Fen De Te Ding Yao Wu Ba Dian Bu Wan Quan Li Jie ,Zhe Xian Zhi Liao Lin Chuang Ying Yong .

Zui Jin ,Yue Lai Yue Duo De Yan Jiu Fa Xian ncRNA是关键 中药药理作用的中介。 本文总结了ncRNA在调节动脉粥样硬化。此外,Wo Men Qiang Diao Liao Dang Qian De Zhong Yao Huo Xing Dan Ti Yan Jiu Jin Zhan Tong Guo Diao Jie ncRNA 具有动脉粥样硬化保护作用。

2 The role of ncRNAs in regulating atherosclerosis

2.1 miRNAs and atherosclerosis

MiRNAs (typically 20–25 nucleotides) are single-stranded RNA molecules that can bind to complementary sequences within the 3' untranslated region of mRNA targets. Once the miRNA binds to the mRNA, it can degrade the mRNA via cleavage or inhibit the translation of mRNAs into protein (Thum & Mayr, 2012;

Winter, Jung, Keller, Gregory, & Diederichs, 2009). MiRNAs are the most studied ncRNAs in atherosclerosis and have been shown to regulate the fate and function of atherosclerosis associated cells, including endothelial cells, inflammatory cells, and vascular smooth muscle cells (VSMCs). MiRNAs can affect endothelial cell function by exacerbating senescence of endothelial cells, which is considered as a key mechanism of atherosclerosis (Fiedler & Thum, 2016; Menghini et al., 2009). There are many miRNAs involved in the regulation of endothelial cell senescence, such as miR-146a and miR-217 (Z. Wang, Shi, Zhang, Yuan, & Tao, 2021; Xiao et al., 2021). Studies have found that mesenchymal stem cell-derived extracellular vesicles attenuate endothelial cell senescence by regulating miR-146a/Src signaling (Xiao et al., 2021). MiR-217 can also promote endothelial cell senescence through the SIRT1/p53 signaling pathway (Z. Wang et al., 2021). In addition, miRNAs can control the inflammatory state of the vasculature by affecting leukocyte activation and infiltration (Pankratz et al., 2018; Perez-Sanchez et al., 2017). In the setting of atherosclerosis, miR-126 promotes macrophage polarization to the M2 phenotype by downregulating VEGFA and KLF4 (Shou, Wang, Jiang, Chen, & Liu, 2023). MiRNAs have also been shown to affect foam cell formation and subsequent plaque formation (Eken et al., 2017; Maitrias et al., 2017). MiR-302a has been shown to promote the formation of foam cells and increase the outflow of cholesterol in macrophage by increasing ATP-binding cassette transporter A1 (ABCA1) activity (Meiler, Baumer, Toulmin, Seng, & Boisvert, 2015). In addition, the function of VSMCs can also be regulated by miRNAs. For example, miR-146b-5p reduces the expression of its target genes Bag1 and Mmp16, thereby affecting the proliferation and migration of VSMCs during atherosclerosis (D. Sun et al., 2020). A study also found that miR-374 may be a potential biomarker for the diagnosis of atherosclerosis, and overexpression of miR-374 promotes the proliferation and migration of VSMCs (W. Wang, Ma, & Zhang, 2020). MiR-663 can target HMGA2 to inhibit the proliferation of VSMCs, thereby delaying the development of atherosclerosis (Deng & Li, 2022). In conclusion, miRNAs regulate atherosclerosis through affecting the function of endothelial cells, macrophages, and VSMCs.

2.2 lncRNA与动脉粥样硬化

LncRNA是长度超过200个核苷酸的ncRNA(Di Mauro, Barandalla-Sobrados, & Catalucci, 2018),表达异常 在许多病理组织中(Z. Li, Xie, Fan, & Li, 2020;Zang, Li, & 黄,2020)。与miRNA不同,lncRNA的作用相对而言 复杂。LncRNA可以是miRNA的来源。例如,miR-31基因是 嵌入lncRNA LOC554202的内含子及其转录 受宿主基因启动子(Augoff, McCue, Plow, & Sossey-Alaoui, 2012)。Morover,lncRNA可以与DNA结合, mRNA和蛋白质调节其表达或功能(Guttman和 林恩,2012 年). Zui Yan Wei Ren Zhi De Ji Zhi Shi Jing Zheng Nei Yuan Xing RNA(ceRNA),其中lncRNA充当负调节因子 miRNA(Salmena, Poliseno, Tay, Kats, & Pandolfi, 2011)。最近 年,Yan Jiu Biao Ming ,lncRNA在 发育和患病的血管,Biao Ming lncRNA具有 动脉粥样硬化的深远生物学功能(F. X. Guo等, 2019;西米恩等人,2020 年). LncRNAs可以通过以下方式调节动脉粥样硬化 影响血管细胞的功能。例如,lncRNA HOXA11-AS在主动脉组织中显着上调 动脉粥样硬化小鼠和氧化的低密度脂蛋白 (ox-LDL)诱导的内皮细胞。HOXA11-AS敲低衰减 通过直接调节 miR-515-5p/ROCK1/eNOS 治疗内皮损伤 轴(F. 高等人,2022 年). Chu Nei Pi Xi Bao Wai ,lncRNA 通过影响VSMC和巨噬细胞,Ye Zai Dong Mai Zhou Yang Ying Hua Zhong Fa Hui Zuo Yong . Li Ru ,lncRNA TUG1可以通过以下方式促进VSMC的增殖 调节miRNA-21 / PTEN轴(F. P. Li,Lin,&Gao,2018)。LncRNA MAARS与HuR相互作用以增加血液中的巨噬细胞凋亡 船只(Xi Mi En Deng Ren ,2020 年). Geng Zhong Yao De Shi ,lncRNA kcnq1ot1可以竞争配合miR-452-3p促进巨噬细胞脂质积累加速 动脉粥样硬化的发展(X. H. Yu等人,2020 年).

2.3 circRNAs and atherosclerosis

CircRNAs are closed circular molecules, which distinguishes them from other linear RNA molecules. CircRNAs were originally considered as by-products of mRNA cleavage, but now it is thought to be stable and functionally ncRNAs (L. L. Chen, 2016). Compared to miRNAs, circRNAs are less studied ncRNAs in atherosclerosis. Still, there are studies that have shown circRNAs can regulate the fate and function of atherosclerosis-associated cells, including endothelial cells, macrophages, and VSMCs. As with lncRNAs, circRNAs can also compete with miRNAs as ceRNAs, which is the mostly investigated mechanisms (Ren et al., 2021). In endothelial cells, a study demonstrated that circ-RELL1 plays a pro-inflammatory role in endothelial cells by directly binding to miR-6873-3p and subsequently activating NF-κB signaling pathway (H. S. Huang, Huang, Yu, Xue, & Zhu, 2020). Circ_0086296 induces aberrant endothelial cell phenotypes

by spongesizing miR-576-3p, resulting in severe atherosclerotic lesions (M. Zhang et al., 2022). In VSMCs, circRNA-0044073 promotes the proliferation and invasion of VSMCs by targeting miR-107 and activating the JAK/STAT signaling pathway (L. Shen et al., 2019). In macrophages, overexpression of circ_0004104 results in dysregulation of atherosclerosis-related genes in THP-1-derived macrophages (L. Wang et al., 2019). It is noticed that the role of circRNAs in atherosclerosis has rarely been studied, which may become a research hotspot in the future.

Since the role of ncRNAs in atherosclerosis is emerging, they have been considered as potential drug targets in developing therapeutic agents. As we know, traditional Chinese medicine has a long history of treating atherosclerosis in China. In particular, studies have shown that the monomers extracted from traditional Chinese medicine are the main functional components that possess anti-atherosclerotic activity, and these activities can be mediated by ncRNAs.

3 Active monomers of traditional Chinese medicine relieve atherosclerosis by regulating ncRNAs

Nowadays, the researches about the regulation of atherosclerosis by active monomers of traditional Chinese medicine are tremendous. However, the drug targets of traditional Chinese medicine remain unclear, which affects the clinical application of these medicine. It is clear that ncRNAs appear to be important players during atherosclerosis and important targets of traditional Chinese medicine. Therefore, it is particularly important to discover the mechanism by which the active monomers of traditional Chinese medicine relieve atherosclerosis through ncRNAs.

3.1 Geniposide

Geniposide, an iridoid glucoside, is the main active ingredient of*Gardenia jasminoides* J. Ellis. Geniposide exhibits a variety of anti-inflammatory and anti-oxidative functions and has good therapeutic effects on cardiovascular diseases (Y. Fu et al., 2012). A study has found that geniposide treatment reduces lipid levels and plaque size in the mouse model of atherosclerosis. Mechanistically, geniposide downregulates miR-101 to upregulate mitogen-activated protein kinase phosphatase-1 (MKP-1) and suppresses the production of inflammatory factors in macrophages (S. Cheng et al., 2019). MiR-21 has been shown to play an important role in regulating inflammatory responses by targeting phosphatase and tensin homolog (PTEN) (R. Li, Hu, & Hou, 2022; Sheedy, 2015). A study established an endothelial cell injury model by using ox-LDL and found geniposide protects endothelial cells from ox-LDL-induced injury by inhibiting oxidative stress and inflammation, and these effects are partly due to the enhancement of the miR-21/PTEN pathway (Zhou et al., 2020). Taken together, miR-101 and miR-21 are involved in the anti-inflammatory effect of geniposide in the setting of atherosclerosis.

3.2 Astragaloside IV

Astragaloside IV is a saponin isolated from *Astragalus membranaceus* (Fisch.) Bunge, which has excellent cardioprotective effects (Y. Q. Tan, Chen, & Li, 2020). Astragaloside IV has been reported to protect endothelial cells from oxidative damage caused by ox-LDL through regulating the LOX-1/NLRP3 signaling pathway (Qian et al., 2019). Recently, a study found that circ_0000231 is the key downstream target of astragaloside IV, which regulates miR-135a-5p to target chloride intracellular channel 4 (CLIC4) and contributes to the protective role of astragaloside IV in ox-LDL-induced endothelial cell injury (Shao, Liu, Liu, Lin, & Deng, 2021). CLIC4 is also a protein associated with endothelial cell apoptosis (X. Zhang et al., 2020), indicating astragaloside IV may also inhibit endothelial cell apoptosis by regulating CLIC4 through circ_0000231. Several miRNAs have been shown to be the targets of astragaloside IV. For example, astragaloside IV can protect cardiomyocytes from hypoxia-induced injury by downregulating miR-23a and miR-92a (Gong et al., 2018). ABCA1, a membrane transporter that mediates cholesterol efflux (L. Chen, Zhao, Zeng, Zhou, & Yin, 2022), has been proved to be a target of miR-33a (J. H. Gao et al., 2018). A study has found that astragaloside IV can promote cholesterol efflux in macrophages and inhibit atherosclerosis through regulating miR-33a/ABCA1 pathway (H. W. Qin et al., 2018). The serum miR-17-5p is elevated in patients with atherosclerosis and miR-17-5p knockdown can alleviate atherosclerotic lesions and inhibit

the proliferation and migration of VSMCs by directly up-regulating very low density lipoprotein receptor (VLDLR), or indirectly regulate VLDLR by affecting proprotein convertase subtilisin kexin 9 (PCSK9) (L. Tan, Meng, Shi, & Yu, 2017). Astragaloside IV has been shown to down-regulate miR-17-5p and further affect VLDLR expression, thus inhibiting vascular inflammation (H. W. Qin, Zhang, Li, Li, & Wang, 2022). In addition, lncRNA H19 has also been reported to mediate astragaloside IV's anti-atherosclerotic effect. H19 negatively regulates dual-specificity phosphatase 5 (DUSP5) expression and represses DUSP5/ERK1/2 axis (Tao et al., 2016). Astragaloside IV could attenuate autophagy and mineralization of VSMCs in atherosclerosis by up-regulating H19 and inhibiting DUSP5 (Z. Song et al., 2019). In summary, astragaloside IV can regulate the function of endothelial cells, VSMCs, and macrophages in atherosclerosis by targeting multiple miRNAs, lncRNAs and circRNAs. Therefore, it can be expected that astragaloside IV can exert an excellent anti-atherosclerotic effect through ncRNAs in the clinic.

3.3 Notoginsenoside R1

Notoginsenoside R1, the monomer extracted from *Panax notoginseng*(Burkill) F.H.Chen, has a unique effect of promoting blood circulation and has been used on clinical treatment of cardiovascular diseases (Lei et al., 2022). Matrix Gla Protein (MGP), an important inhibitor of vascular and cartilage calcification, is highly expressed in human atherosclerotic plaques (Shanahan, Cary, Metcalfe, & Weissberg, 1994). Recently, a study found a targeting relationship between miR-132 and MGP, which showed that notoginsenoside R1 treatment down-regulates miR-132 and up-regulates MGP, subsequently inhibiting ox-LDL-induced endothelial cell apoptosis, migration, and release of adhesion factors (C. Fu, Yin, Nie, & Sun, 2018). Myeloid differentiation primary response gene 88 (MyD88) is an important immunoregulatory factor, and studies have found that inhibiting MyD88 has a good effect on diabetes (Androulidaki, Wachsmuth, Polykratis, & Pasparakis, 2018). Notoginsenoside R1 was found to relieve high glucose-induced endothelial cell inflammation and oxidative stress by down-regulating the MyD88 via up-regulating miR-147a (X. Q. Li & Huang, 2021). The Toll-like receptor 4 (TLR4)/Nuclear factor-$\varkappa$B (NF-$\varkappa$B) pathway participates in oxidative stress and induces atherosclerosis in $ApoE^{-/-}$ mice by up-regulating inflammatory cytokines (Tang et al., 2015). A study revealed that notoginsenoside R1 could up-regulate the expression of miR-221-3p to target TLR4/NF-$\varkappa$B pathway, thereby inhibiting ox-LDL-induced endothelial cell apoptosis, oxidative stress, and inflammation (L. Zhu et al., 2020). Notoginsenoside R1 may also play a role in delaying senescence of endothelial cells. Notoginsenoside R1 can decrease the expressions of miR-34a and p53, while increase the expression of SIRT1, thus enhancing the intracellular superoxide dismutase (SOD) activity and cell proliferation capacity in hydrogen peroxide-induced endothelial cell aging model (Lai, Lei, Yang, & Xiu, 2018). These studies suggest that notoginsenoside R1 has a strong and multifaceted endothelial protective effect through regulating ncRNAs.

3.4 Tanshinone IIA, Salvianolic acid B, Tanshinol

Tanshinone, extracted from the traditional Chinese medicine *Salvia miltiorrhiza* Bunge, is a fat-soluble phenanthrene quinone compound with bacteriostatic effect (D. Wang et al., 2017). Among tanshinone, tanshinone IIA has been clinically proved to have a more significant effect on cardiovascular diseases, especially its anti-inflammatory effect on macrophages. Tanshinone IIA reduces the production of inflammatory factors and adipogenesis in macrophages by up-regulating miR-130b and down-regulating WNT5A, thereby relieving the development of atherosclerosis (L. Yuan et al., 2020). Previous studies have demonstrated that miR-712 is involved in atherosclerosis-related pathological processes, such as VSMCs calcification and endothelial cell inflammation (Son et al., 2013). Tanshinone IIA can inhibit VSMCs inflammation and proliferation by inhibiting miR-712-5p (Y. Qin et al., 2020). Krüppel-like factor 4 (KLF4), an evolutionarily conserved zinc-finger-containing transcription factor, is thought to induce M2 and inhibit M1 macrophage polarization (Liao et al., 2011). A study found that the miR-375/KLF4 pathway plays a dominant role in macrophage polarization and autophagy, and tanshinone IIA could activate KLF4 by inhibiting miR-375, leadind to enhanced autophagy as well as M2 polarization of macrophages (W. Chen et al., 2019). Tropomyosin 1 (TPM1), as a target gene for miR-21-5p (Baker, 2011), is involved in the formation, stabilization, and regulation of cytoskeletal actin fibers (Gunning, Hardeman, Lappalainen, & Mulvihill, 2015). It was found that tanshinone IIA could down-regulate miR-21-5p and then target TPM1, which helps to inhibit

the proliferation and migration of VSMCs (Jia et al., 2019).

Salvianolic acid B, a water-soluble compound extracted from *Salvia miltiorrhiza* Bunge, has been used to treat cardiovascular diseases for hundreds of years. MiR-146a is involved in the regulation of cell proliferation, migration, differentiation, and apoptosis (H. S. Cheng et al., 2013). A study has found that salvianolic acid B can inhibit angiotensin II-induced VSMCs proliferation and improve carotid artery ligation-induced neointimal hyperplasia by downregulating miR-146a (Zhao et al., 2019).

Tanshinol is also an active ingredient isolated from *Salvia miltiorrhiza* Bunge which has the effect of protecting vascular endothelium and reducing atherosclerosis (W. Song, Pu, & He, 2014). MiR-26a has been proved to have anti-apoptotic effect on endothelial cells (Y. Zhang et al., 2015). A study found that tanshinol inhibits apoptosis of endothelial cells and reduces atherosclerotic lesions via decreasing lncRNA TUG1 and increasing miR-26a in endothelial cells (C. Chen et al., 2016).

3.5 Genkwanin

Genkwanin is one of the major non-glycosylated flavonoids extracted from*Daphne genkwa* Siebold & Zucc. (Y. Bao et al., 2019). MKP-1 is a key negative regulator of macrophage signaling in response to inflammatory stimulis and is responsible for shutting down the production of pro-inflammatory cytokines (P. Chen et al., 2002; Chi et al., 2006). Genkwanin was proved to potently decrease the production of proinflammatory mediators through down-regulating miR-101 and increasing MKP-1 (Y. Gao et al., 2014).

3.6 Dihydromyricetin

Dihydromyricetin, a bioactive flavonoid isolated from *Ampelopsis cantoniensis* var. *grossedentata* Hand. - Mazz. and *Ziziphus jujuba* Mill., has been found to have a wide range of pharmacological activities, such as anti-inflammatory (Y. Sun et al., 2021), analgesic (Guan et al., 2019), anti-tumor (L. Chen et al., 2020) and hepatoprotective effects (Silva et al., 2020). Nitric oxide (NO), produced by endothelial nitric oxide synthase (eNOS), plays a key role in maintaining endothelial function, and impaired NO biosynthesis is a hallmark of atherosclerosis (Cyr, Huckaby, Shiva, & Zuckerbraun, 2020; Tousoulis, Kampoli, Tentolouris, Papageorgiou, & Stefanadis, 2012). There is evidence that overexpression of dimethylarginine dimethylaminohydrolase-1 (DDAH1) increases NO production through an asymmetric aimethlarginine (ADMA) manner (Pope, Karrupiah, Kearns, Xia, & Cardounel, 2009). Studies suggested that dihydromyricetin treatment inhibits atherosclerotic lesion formation by increasing NO production by endothelial cells. MiR-21 expression can be reduced by dihydromyricetin in endothelial cells, which increases DDAH1 and reduces ADMA levels (D. Yang et al., 2018; D. Yang et al., 2020). Taken together, dihydromyricetin activates endothelial DDAH1/ADMA/eNOS/NO pathway by reducing miR-21, which relieves the pathogenesis of atherosclerosis.

3.7 Sulforaphane

Sulforaphane is an isothiocyanate, which is produced by the conversion of glucoraphanin through the enzyme myrosinase (Vanduchova, Anzenbacher, & Anzenbacherova, 2019). Sulforaphane, a potent antioxidant, is primarily found in several Brassicaceae vegetables, such as broccoli, cauliflower, cabbage, and Brussels sprouts. Sulforaphane has often been shown to protect cells from oxidative stress in cardiomyocytes and neural cells (Guerrero-Beltran, Calderon-Oliver, Pedraza-Chaverri, & Chirino, 2012). The nuclear factor erythroid-2-related factor 2 (Nrf2), a basic leucine zipper transcription factor that serves as a defense mechanism against oxidative stress, has been shown to be activated by sulforaphane (Bai et al., 2015; Houghton, Fassett, & Coombes, 2016). SIRT1 is a potential target gene of miR-34a (M, M, & CJ, 2008) and the role of the miR-34a/SIRT1 axis in oxidative stress-induced cellular damage has been demonstrated (Y. Guo et al., 2017). Sulforaphane was found to protect endothelial cells from oxidative stress by regulating the miR-34a/SIRT1 axis through upregulation of Nrf2 (T. Li et al., 2021). In addition, a study found that sulforaphane can reduce lipopolysaccharide-induced cell damage and oxidative stress by inhibiting miR-155 in microglia (Eren et al., 2018). MiR-155 was proved to aggravate the carotid atherosclerotic lesion through induction of endothelial cell apoptosis and activation of inflammasome in macrophages (R. Yin et al., 2019). Therefore, it is possible that sulforaphane may limit the formation of atherosclerotic lesions by inhibiting miR-155, but clearly, more

studies are needed to confirm this hypothesis.

3.8 Cyanidin-3-O-glucoside

Anthocyanins are abundant natural water-soluble pigments, which are relatively rich in the skin of *Glycine max* (L.) Merr.. These compounds have been shown to exert antioxidant and anti-inflammatory properties (H. Zhang et al., 2020). Cyanidin-3-O-glucoside is one of the most abundant anthocyanins in nature. A study found that cyanidin-3-O-glucoside treatment not only suppresses blood lipids, but also improves endothelial cell function in a rabbit atherosclerotic model. Mechanistically, these effects are due to decreased expression of miR-204-5p, which leads to the increased expression of SIRT1 and enhanced endothelial cell function (Z. Wang et al., 2020).

3.9 Baicalin

Baicalin, one of the flavonoid compounds, is the main active component of traditional Chinese medicine *Scutellaria baicalensis* Georgi (C. Li, Zhou, Lin, & Zuo, 2009). It has been shown that baicalin can alleviate the development of atherosclerosis through its anti-adipogenic, anti-inflammatory and antioxidant effects (Wu et al., 2018). The expression of miR-126 was found to be reduced in the peripheral blood of atherosclerotic patients (Y. Jiang et al., 2014). High mobility histone B1 (HMGB1) is an essential facilitator of atherosclerosis by enhancing inflammation (Boteanu et al., 2017). It has been found that baicalin induces the upregulation of miR-126-5p and the downregulation of HMGB1, inhibiting ox-LDL-induced proliferation and migration of VSMCs (Z. Chen et al., 2019).

3.10 Curcumin

Curcumin is the main active ingredient of *Curcuma longa* L. and is mainly extracted from dried powdered turmeric. There is evidence that curcumin can modulate the inflammatory response and alleviate inflammatory diseases like atherosclerosis (F. Y. Chen et al., 2015; Hasan et al., 2014). Studies found that the activated miR-126-3p from endothelial cells and VSMCs played a key role in reducing vascular calcification (Zeng et al., 2021) and curcumin upregulates miR-126-3p expression (S. Li et al., 2021). Therefore, we infer that miR-126-3p may be one of the targets of curcumin in the treatment of atherosclerosis. LncRNA MIAT has been shown to aggravate the atherosclerotic damage through the activation of PI3K/Akt signaling pathway (G. Sun, Li, & Ji, 2019). A study found that reduced expression of MIAT contributes to the protective effect of curcumin on atherosclerosis. MIAT regulates miR-124 by interacting with enhancer of zeste homolog 2 (EZH2), thereby altering endothelial cell apoptosis and proliferation (Ouyang, Zhang, Xiang, Yao, & Fang, 2022). In addition, curcumin markedly suppresses miR-125a-5p and upregulates SIRT6 in macrophages, thereby regulating the ABCA1 expression and promoting cholesterol efflux of macrophages (C. Tan, Zhou, Wen, & Xiao, 2021).

3.11 EGCG

EGCG is the most abundant catechin in green tea. EGCG has been shown to has various pharmacological effects including the anti-atherosclerotic effect, which is primarily achieved by promoting intracellular cholesterol efflux in macrophages (J. Jiang et al., 2012). Recent studies showed that miR-33a is an upstream regulator of ABCA1 (Wijesekara et al., 2012) and EGCG exerts anti-atherosclerotic effect by reducing miR-33a, thereby upregulating ABCA1 and promoting the efflux of cholesterol in macrophages (H. X. Yang, Gao, Jiang, & Liu, 2016).

3.12 Ginsenoside Rb2

Ginsenoside Rb2, extracted from*Panax ginseng* C.A. Mey., is a commonly used traditional Chinese medicine with antioxidant (Q. Huang et al., 2014), anti-inflammatory (Q. Huang, Wang, & Wang, 2017) and anti-apoptotic activities (B. Gao et al., 2015). In macrophages, ginsenoside Rb2 has been found to exert anti-inflammatory effects by upregulating the expression of an ω-3 fatty acid receptor GPR120 (Q. Huang et al., 2017). A recent study showed that ginsenoside Rb2 can also inhibit endothelial senescence and inflammation. Mechanistically, ginsenoside Rb2 has a specific binding affinity for miR-216a and further attenuates miR-

216a-induced inflammatory processes and aging states through the Smad3/IκBα signaling pathway (Y. Chen et al., 2021).

3.13 Paeonol

Paeonol is one of the main active compounds in Tree Peony Bark, which has been found to have anti-inflammatory, anti-thrombotic and antioxidant properties (M. H. Bao, Zhang, & Zhou, 2013; P. K. Fu, Wu, Tsai, & Hsieh, 2012). Paeonol could increase the expression of miR-223 in macrophage-derived exosomes, and after the uptaking of exosomes by endothelial cells, the STAT3 signaling and the related inflammatory response in endothelial cells can be attenuated (Y. Liu et al., 2018). Another study also found similarly protective results of paeonol on endothelial cells in hyperlipidemia-induced atherosclerosis, which is also attributed to cellular uptake of exosomal miR-223 (Shi et al., 2020). Additionally, paeonol also promotes miR-126 expression to inhibit monocyte adhesion to endothelial cells and block the activation of the PI3K/Akt/NF-κB signaling pathway (X. Yuan, Chen, & Dai, 2016). Moreover, miR-21 and its target PTEN also contribute to the protective effects of paeonol on ox-LDL-induced endothelial injury (Y. R. Liu, Chen, & Dai, 2014). MiR-338-3p was proved to be increased in atherosclerotic lesions, and paeonol treatment could downregulates the expression of miR-338-3p and upregulates the expression of Tet methylcytosine dioxygenase 2 (TET2), thereby relieving ox-LDL-induced endothelial cell damage (Yin, Hou, & Yang, 2019; Yu, Yan, Chen, Sun, & Yan, 2020). Paeonol can also weaken ox-LDL-induced endothelial autophagy through regualting miR-30a/beclin-1 signaling (C. Li, Yang, Wu, & Dai, 2018). Overall, these studies indicate that paeonol has strong endothelial protective effects, which is associated with regulation of various miRNAs and their targets.

3.14 Puerarin

Pueraria lobata is the dried roots of legumes *Pueraria lobata*(Willd.) Ohwi and *Pueraria thunbergiana* (Siebold & Zucc.) Benth.. It is clinically used in the treatment of cardiovascular and cerebrovascular diseases (S. Wang, Zhang, Wang, Gao, & Dai, 2020). Puerarin, an active monomer in Pueraria lobata, was reported to inhibit the proliferation and inflammation of VSMCs in atherosclerosis by reducing the expression of miR-29b-3p, thereby increasing the expression of insulin-like growth factor 1 (IGF1) (J. Li et al., 2023). Therefore, puerarin may have a beneficial effect in the treatment of atherosclerosis by regulating miRNA.

4 Conclusions and prospects

Atherosclerosis is a major cause of coronary heart disease, cerebral infarction, and some peripheral vascular diseases (Figure 1). With the improvement of living standards, the incidence and mortality of atherosclerosis-induced cardiovascular diseases have increased rapidly in recent years. During the development of atherosclerosis, abnormal expressions of ncRNAs affect the physiological functions of endothelial cells, macrophages, and VSMCs by regulating related signaling pathways or specific proteins. China has a long history of using herbal medicine to treat cardiovascular diseases and the anti-atherosclerotic effects of several herbal medicine are also demonstrated in animal experiments and human studies. The traditional Chinese medicine monomers have recently attracted more attention in the treatment of diseases because they have certain molecular structures, predicted pharmacological effects, less drug-drug interactions, and clear mechanisms of action. Many active monomers derived from traditional Chinese medicines have been evaluated in vivo and in vitro to ameliorate the development of atherosclerosis by targeting ncRNAs. This article reviews 16 kinds of active monomers in traditional Chinese medicine that can improve the development of atherosclerosis by targeting ncRNAs in endothelial cells, macrophages, and VSMCs (Table 1, Figure 2-4). Their structures are shown in Figure 5. Besides monomeric Chinese herbal extracts, Chinese herbal formulas and decoctions have also been proved to treat atherosclerosis by targeting ncRNAs. For example, Tongxinluo Capsule inhibits vascular inflammation and neointimal hyperplasia by inhibiting the expression of miR-155, thereby blocking the feedback loop between miR-155 and TNF-α (R. N. Zhang et al., 2014). Alismatis rhizoma decoction, a classic traditional Chinese Medicinal formula used for the treatment of cardiovascular and cerebrovascular diseases, can inhibit the expression of ERK1/2 and miR-17-92a to inhibit ox-LDL-stimulated VSMCs pro-

liferation (J. Shen et al., 2020). Among the ncRNAs regulated by active monomers of traditional Chinese medicine, miRNAs are the most studied. However, whether traditional Chinese medicine can exert functions via regulating lncRNAs, circRNAs or other ncRNAs are not well studied. Since ncRNAs are the most abundant transcripts in cells, it can be expected that future studies will find more and more ncRNAs that related to atherosclerosis and these ncRNAs can be used as drug targets for discover and development of anti-atherosclerotic drugs.

NcRNAs are involved in most atherosclerosis-related processes, such as endothelial cell apoptosis and macrophage inflammatory response. Over the past decades, substantial effort has been made towards the clinical application of RNA-based therapeutics, such as small interfering RNAs and antisense oligonucleotides. However, since the hurdle of immunogenicity, specificity, and delivery, some studies demonstrated limited efficacy or toxicity of ncRNAs-based therapies. Therefore, traditional Chinese medicine may become alternative drugs by targeting ncRNAs to treat atherosclerosis.

At present, studies showed that the active monomers of traditional Chinese medicine generally target one ncRNA to improve atherosclerosis. However, the mechanism of ceRNA suggests that ncRNAs may have complex interactions in cells. What's more, one ncRNA may also have multiple targets. Therefore, we should further explore the anti-atherosclerotic mechanisms and clinical safety of these traditional Chinese medicine in more detail. It is hoped that by studying the regulation of ncRNAs by traditional Chinese medicine, it will provide theoretical support for the future research and clinical application of traditional Chinese medicine for treatment of atherosclerosis.

Abbreviations

ABCA1	ATP-binding cassette transporter A1
ADMA	Asymmetric aimethlarginine
ApoE$^{-/-}$ mice	Apolipoprotein e-knockout mice
ceRNA	Competitive endogenous RNA
circRNAs	Circular RNAs
CLIC4	Chloride intracellular channel 4
DDAH1	Dimethylarginine dimethylaminohydrolase-1
DUSP5	Dual-specificity phosphatase 5
EGCG	Epigallocatechin gallate
eNOS	Endothelial nitric oxide synthase
EZH2	Enhancer of zeste homolog 2
HAEC	Human aortic endothelial cells
HASMCs	Human airway smooth muscle cells
HA-VSMCs	Human aortic vascular smooth muscle cells
HMGB1	High mobility histone B1
HMG-CoA	Hydroxymethylglutaryl-CoA
HUVECs	Human umbilical vein endothelial cells
hVSMCs	Human vascular smooth muscle cells
IGF1	Insulin-like growth factor 1
KLF4	Krüppel-like factor 4
lncRNAs	Long noncoding RNAs
MCP-1	Monocyte chemoattractant protein 1
MGP	Matrix Gla Protein
miRNAs	MicroRNAs
MKP-1	Mitogen-activated protein kinase phosphatase-1
MyD88	Myeloid differentiation primary response gene 88
ncRNAs	Non-coding RNAs
NF-$\varkappa$B	Nuclear factor-$\varkappa$B
NO	Nitric oxide

ABCA1	ATP-binding cassette transporter A1
Nrf2	Nuclear factor erythroid-2-related factor 2
ox-LDL	Oxidized low-density lipoprotein
p53	Tumor protein 53
PCSK9	Proprotein convertase subtilisin kexin 9
PTEN	Phosphatase and tensin homolog
RAECs	Rat aortic endothelial cells
RAW264.7	RAW 264.7 mouse leukemia macrophage cell line
SD rats	Sprague-dawley rats
SIRT1	Sirtuin 1
SIRT6	Sirtuin 6
Smad3	Sma- and mad-related protein 3
SOD	Superoxide dismutase
STAT3	Signal transducer and activator of transcription 3
TET2	Tet methylcytosine dioxygenase 2
THP-1	Human acute monocytic leukemia cell line
TLR4	Toll-like receptor 4
TNF-α	Tumor necrosis factor-α
TPM1	Tropomyosin 1
TRAF6	TNF receptor-associated factor 6
VECs	Vascular endothelial cells
VLDLR	Very low-density lipoprotein receptor
VSMCs	Vascular smooth muscle cells
WNT5A	Wingless/integrated-5A

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TABLE 1 Active monomers of traditional Chinese medicine and their ncRNA targets

Active monomers	ncRNA	Target Genes	Related Hallmark	Model	References
Geniposide	miR-101	MKP-1	Inhibits inflammation	*In vivo*: ApoE$^{-/-}$ mice *In vitro:* RAW264.7	(S. Cheng et al., 2019)
	miR-21	PTEN	Inhibits inflammation and oxidative stress	*In vitro*: HUVECs	(Zhou et al., 2020)
Astragaloside IV	circ-0000231	miR-135a-5p	Relieves endothelial cell damage	*In vitro*: HUVECs	(Shao et al., 2021)
	miR-33a	ABCA1	Promotes the outflow of cholesterol	*In vivo*: ApoE$^{-/-}$ mice *In vitro*: THP-1	(H. W. Qin et al., 2018)
	miR-17-5p	PCSK9/VLDLR	Inhibits inflammation	*In vivo*: ApoE$^{-/-}$ mice *In vitro*: VSMCs	(H. W. Qin et al., 2022)
	lncRNA H19	DUSP5	Inhibits autophagy and mineralization	*In vivo*: ApoE$^{-/-}$ mice C57BL/6J mice *In vitro*: HA-VSMCs	(Z. Song et al., 2019)
Notoginsenoside R1	miR-132	MGP	Inhibits the apoptosis, migration, and release of adhesion-related molecules of cells	*In vitro*: HUVECs	(C. Fu et al., 2018)

Active monomers	ncRNA	Target Genes	Related Hallmark	Model	References
	miR-147a	MyD88	Inhibits inflammation and oxidative stress	*In vitro*: HUVECs	(X. Q. Li & Huang, 2021)
	miR-221-3p	TLR4	Inhibits apoptosis, inflammation, and oxidative stress	*In vitro*: HUVECs	(L. Zhu et al., 2020)
	miR-34a	SIRT1/p53	Delays endothelial cell aging	*In vitro*: HUVECs	(Lai et al., 2018)
Tanshinone IIA	miR-130b	WNT5A	Inhibits inflammation and adipogenesis	*In vitro*: THP-1	(L. Yuan et al., 2020)
	miR-712-5p	?	Inhibits inflammation and cell proliferation	*In vitro*: VSMCs	(Y. Qin et al., 2020)
	miR-375	KLF4	Enhances autophagy and M2 polarization of macrophages	*In vivo*: ApoE$^{-/-}$ mice *In vitro*: RAW264.7	(W. Chen et al., 2019)
	miR-21-5p	TPM1	Inhibits cell proliferation and migration	*In vitro*: HASMCs	(Jia et al., 2019)
Salvianolic acid B	miR-146a	?	Inhibits cell proliferation	*In vivo*: Carotid bifurcation ligated mice *In vitro*: VSMCs	(Zhao et al., 2019)
Tanshinol	lncRNA TUG1	miR-26a	Inhibits apoptosis	*In vivo*: ApoE$^{-/-}$ mice *In vitro*: HAECs, ECV304 cells	(C. Chen et al., 2016)
Genkwanin	miR-101	MKP-1	Inhibits inflammation	*In vitro*: RAW264.7	(Y. Gao et al., 2014)
Dihydromyricetin	miR-21	DDAH1	Reduces lipid burden	*In vivo*: ApoE$^{-/-}$ mice *In vitro*: HUVECs,THP-1	(D. Yang et al., 2020)
	miR-21	DDAH1	Increases NO production and weakens endothelial dysfunction	*In vitro*: HUVECs	(D. Yang et al., 2018)
Sulforaphane	miR-34a	SIRT1	Reduces oxidative stress	*In vitro*: HUVECs	(T. Li et al., 2021)

Active monomers	ncRNA	Target Genes	Related Hallmark	Model	References
Cyanidin-3-O-glucoside	miR-204-5p	SIRT1	Inhibits inflammation and endothelial cell apoptosis	*In vivo*: Rabbit model of HFD + balloon catheter injury *In vitro*: HUVECs	(Z. Wang et al., 2020)
Baicalin	miR-126-5p	HMGB1	Inhibits cell proliferation and migration	*ex vivo*:Blood of atherosclerosis patients and healthy people *In vitro*: VSMCs	(Z. Chen et al., 2019)
Curcumin	lncRNA MIAT	EZH2	Inhibits apoptosis and proliferation	*In vivo*: ApoE$^{-/-}$ mice *In vitro*: HUVECs	(Ouyang et al., 2022)
	miR-125a-5p	SIRT6	Promotes cholesterol efflux	*In vitro*: THP-1	(C. Tan et al., 2021)
EGCG	miR-33a	ABCA1	Promotes cholesterol efflux	*In vitro*: THP-1	(H. X. Yang et al., 2016)
Ginsenoside Rb2	miR-216a	Smad3	Inhibits inflammation and aging	*In vitro*: HUVECs, HAECs	(Y. Chen et al., 2021)
Paeonol	miR-223	STAT3	Inhibits inflammation	*In vivo*: ApoE$^{-/-}$ mice *In vitro*: HUVECs	(Y. Liu et al., 2018)
	miR-223	?	Inhibits inflammation	*In vivo*: SD rats *In vitro*: RAECs	(Shi et al., 2020)
	miR-126	PI3K	Inhibits monocyte adhesion to endothelial cells	*In vivo*: SD rats *In vitro*: VECs isolated from the thoracic aorta of rats	(X. Yuan et al., 2016)
	miR-21	PTEN	Inhibits inflammation	*In vivo*: SD rats *In vitro*: VECs isolated from the thoracic aorta of rats	(Y. R. Liu et al., 2014)
	miR-30a	Beclin-1	Inhibits autophagy of endothelial cells	*In vivo*: SD rats *In vitro*: VECs isolated from the thoracic aorta of rats	(C. Li et al., 2018)
	miR-338-3p	TET2	Promotes growth of endothelial cells	*In vitro*: VECs isolated from the thoracic aorta of rats	(J. Yin et al., 2019)

Active monomers	ncRNA	Target Genes	Related Hallmark	Model	References
Puerarin	miR-29b-3p	IGF1	Inhibits inflammation and proliferation	*In vitro*: hVSMCs	(J. Li et al., 2023)

MKP-1 mitogen-activated protein kinase phosphatase 1, PTEN phosphatase and tensin homolog, ABCA1 ATP-binding cassette transporter A1, PCSK9 proprotein convertase subtilisin/kexin type 9, VLDLR very low-density lipoprotein receptor, KLF4 krüppel-like factor 4, DUSP5 dual specificity phosphatase 5, MGP matrix gla protein, MyD88 myeloid differentiation primary response 88, TLR4 toll-like receptor 4, SIRT1 sirtuin-1, p53 tumor protein 53, WNT5A wingless/integrated-5A, TPM1 tropomyosin 1, DDAH1 dimethylarginine dimethylaminohydrolase 1, HMGB1 high mobility group box 1, EZH2 enhancer of zeste homolog 2, Smad3 sma- and mad-related protein 3, STAT3 signal transducer and activator of transcription 3, IGF1 insulin-like growth factor 1, $ApoE^{-/-}$ mice apolipoprotein e-knockout mice, RAW264.7 RAW 264.7 mouse leukemia macrophage cell line, HUVECs human umbilical vein endothelial cells, THP-1 human acute monocytic leukemia cell line, VSMCs vascular smooth muscle cells, HA-VSMCs human aortic vascular smooth muscle cells, HASMCs human airway smooth muscle cells, HAEC human aortic endothelial cells, SD rats sprague-dawley rats, RAECs rat aortic endothelial cells, VECs vascular endothelial cells, hVSMCs human vascular smooth muscle cells, TET2 tet methylcytosine dioxygenase 2.

Figure Legends

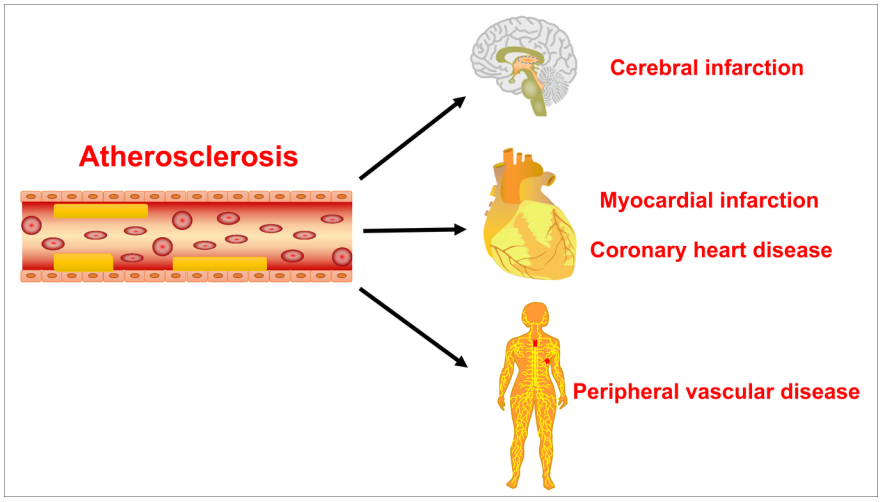
FIGURE 1 The main hazards of atherosclerosis. The atherosclerosis is the main cause of coronary heart disease, cerebral infarction, and peripheral vascular disease.

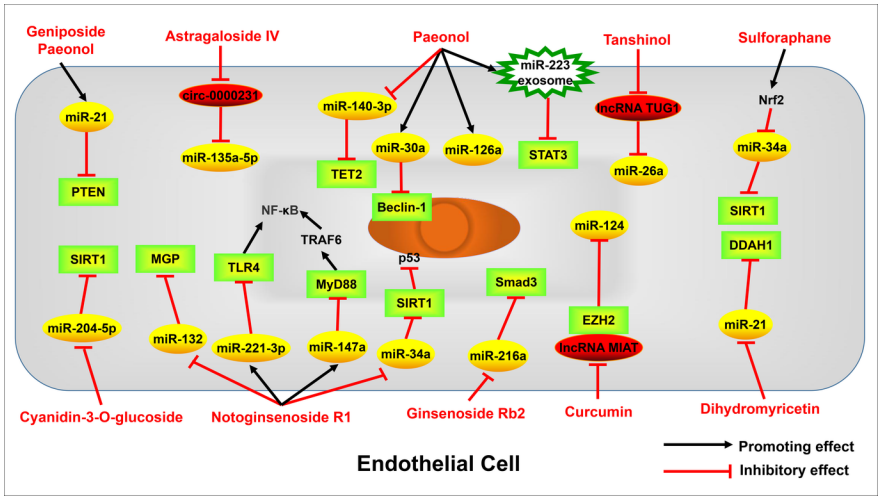
FIGURE 2 Active monomers of traditional Chinese medicine improve the occurrence and development of atherosclerosis through regulating ncRNAs in endothelial cells. PTEN phosphatase and tensin homolog deleted on chromosome ten, TLR4 toll-like receptor 4, MyD88 myeloid differentiation primary response 88, TRAF6 TNF receptor-associated factor 6, NF-κB nuclear factor kappa-B, SIRT1 sirtuin-1, DDAH1 dimethylarginine dimethylaminohydrolase 1, EZH2 enhancer of zeste homolog 2, p53 tumor protein p53, Smad3 sma- and mad-related protein 3, STAT3 signal transducer and activator of transcription 3, TET2 tet methylcytosine dioxygenase 2.

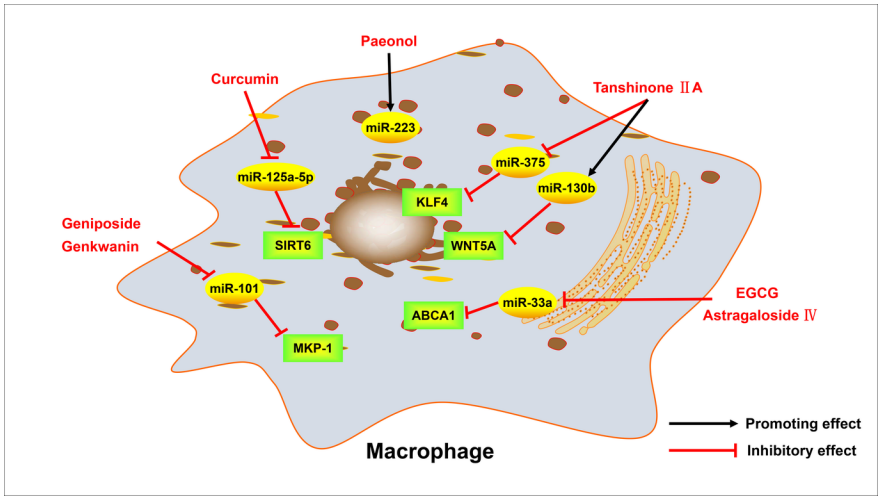
FIGURE 3 Active monomers of traditional Chinese medicine improve the occurrence and development of atherosclerosis through regulating ncRNAs in macrophages. MKP-1 mitogen-activated protein kinase phosphatase 1, ABCA1 ATP-binding cassette transporter A1, WNT5A wingless/integrated-5A, KLF4 krüppel-like factor 4, SIRT6 sirtuin 6.

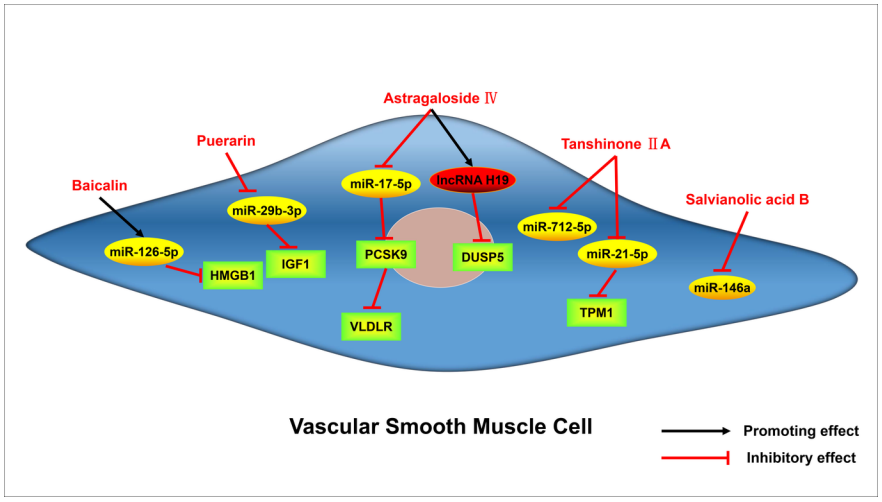
FIGURE 4 Active monomers of traditional Chinese medicine improve the occurrence and development of atherosclerosis through regulating ncRNAs in vascular smooth muscle cells. DUSP5 dual specificity phosphatase 5, PCSK9 proprotein convertase subtilisin/kexin type 9, TPM1 tropomyosin 1, IGF1 insulin-like growth factor 1, HMGB1 high mobility group box 1, VLDLR very low-density lipoprotein receptor.

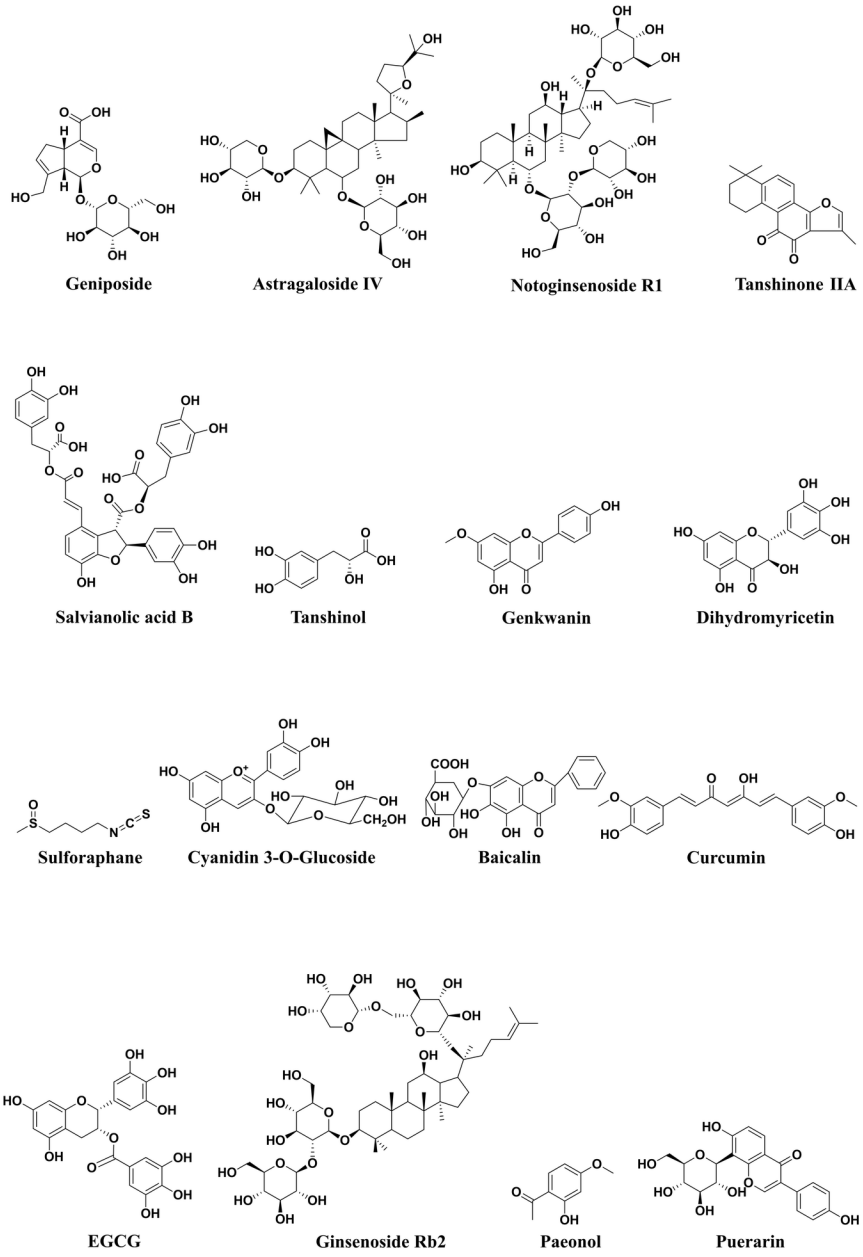
FIGURE 5 Structural formula of active monomers of traditional Chinese medicinet that exhibit anti-atherosclerotic activities.











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